Vitamins B9, B12 & C

Dr Jehad Al-Shuneigat

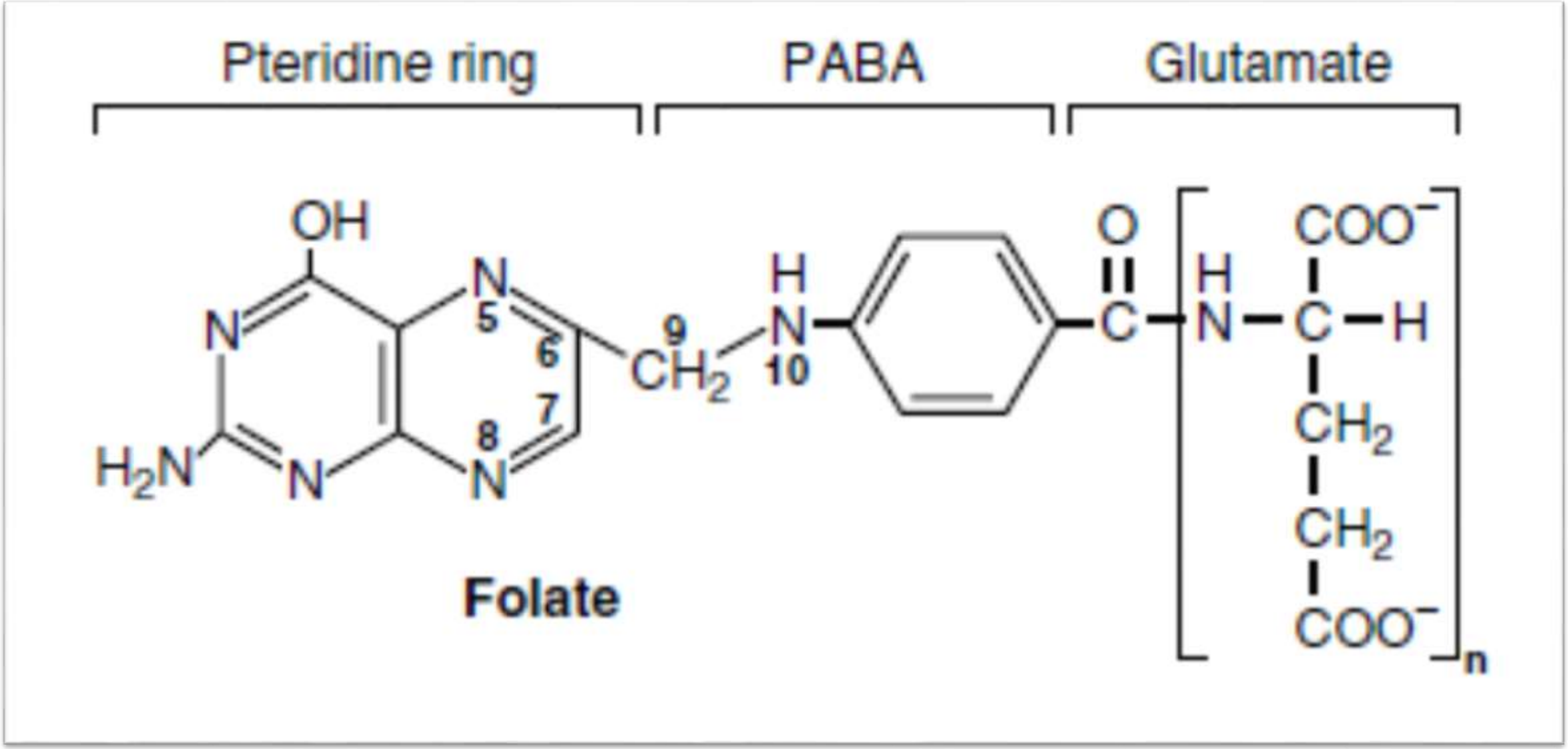
- Vitamins are organic compounds
- They cannot be synthesized in a sufficient amount by the human body; so, they must be obtained from the diet.
- Vitamins are classified as either water-soluble or fat-soluble.
- The fat soluble vitamins include (A, D, E, and K)
- Water soluble vitamins include (B vitamins and vitamin C).
- The water-soluble vitamins easily dissolve in water and are excreted from the body rapidly since they are not stored for a long time, except for vitamin B12. This is why you should get water-soluble vitamins regularly from your diet.
- Fat-soluble vitamins are absorbed in the intestine in the presence of lipid and they are more likely to be stored in the body.

Folate

- Folate also known as vitamin B-9 (previously as folacin) occurs naturally in foods
- Folic acid is the synthetic form of folate used in dietary supplements.
- Folates are synthesized in bacteria and plants and is found mainly in dark green leafy vegetables, beans, peas and nuts. Fruits rich in folate include oranges, lemons, bananas, melons and strawberries.
- Our body is unable to store folate for long periods of time
- Natural folates found in foods are all conjugated to a polyglutamyl chain containing different numbers of glutamic acids depending on the type of food.
- This polyglutamyl chain is removed in the brush border of the mucosal cells by the enzyme folate conjugase, and folate monoglutamate is subsequently absorbed.
- The primary form of folate entering human circulation from the intestinal cells is 5-methyltetrahydrofolate monoglutamate.

- **<u>Folate chemical structure</u>**
- Folates has three major structural components:
- 1. Pteridine ring (molecular formula $C_6H_4N_4$) composed of fused pyrimidine and pyrazine rings.
- 2. Para-aminobenzoic acid (PABA) (NH2-C_6H_4-COOH) made up of benzene ring attached two functional groups COOH and NH2
- 3. Polyglutamate tail consisting of polymer of the amino acid glutamic acid residues (molecular formula $C_5H_9NO_4$).

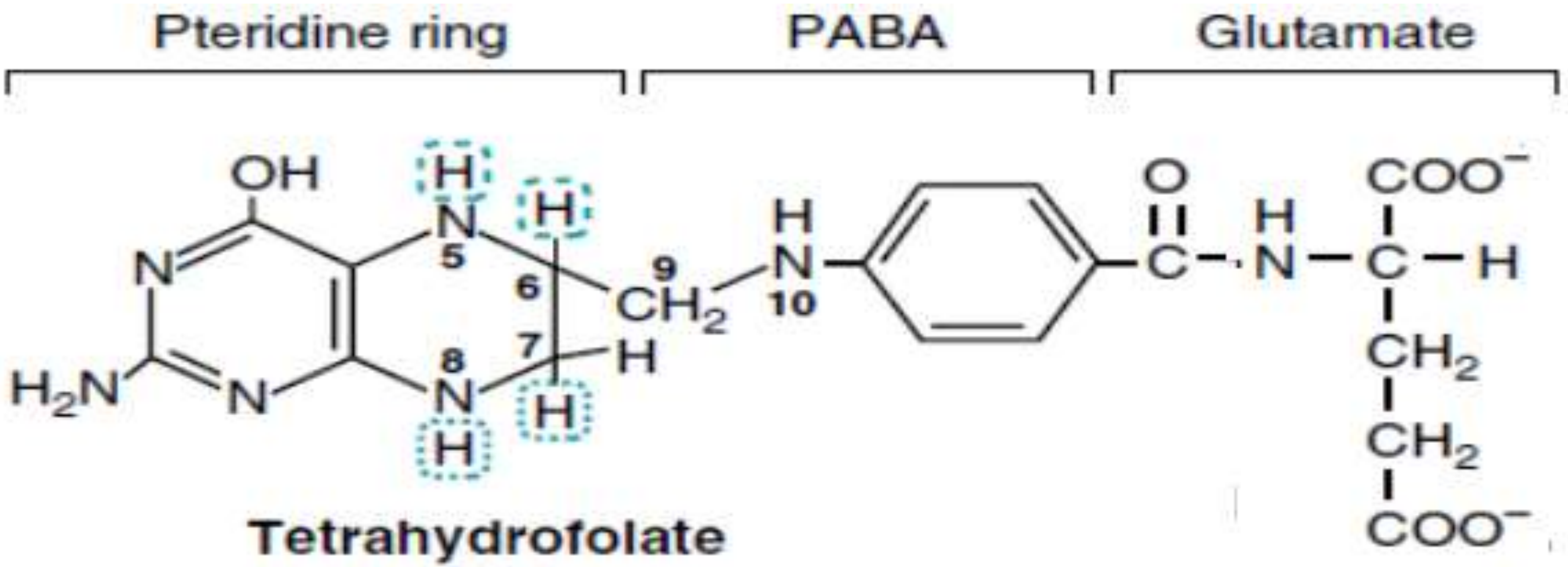
Folate Chemical Structure



Folate Function:

1. Synthesis, repair, and methylation of DNA.
2. A cofactor in many vital biological reactions.
3. Folate has an important role in cell division and it is especially needed during infancy and pregnancy.
4. Production of healthy red blood cells and prevent anemia.

- **<u>Folate activation</u>**
- Folate and folic acid are not active in the body thus they must be reduced to their active form known as tetrahydrofolate (FH4)
- In the liver dihydrofolate reductase, in a two steps reaction, converts folate into dihydrofolate (FH2) then the same enzyme convert dihydrofolate to tetrahydrofolate (FH4) and each step needs NADPH thus the whole reaction require 2NADPH.



Tetrahydrofolate
(FH_4)

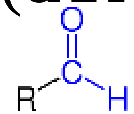
FH4 and the transporting the one-carbon group

The main function of FH4 is transporting the one-carbon group (that is accepted from serine, glycine, histidine, formaldehyde, and formate) to biosynthetic reactions.

The one-carbon group carried by FH4 is bound to N5, or N10, or to both or they form a bridge between N5 and N10.

For example, one-carbon units are transferred to the:

1. Transfer a one-carbon group (as a methyl group) to deoxyuridine monophosphate (**dUMP**) to form deoxythymidine monophosphate (**dTMP**).

2. Transfer a one-carbon group (as a formyl group 

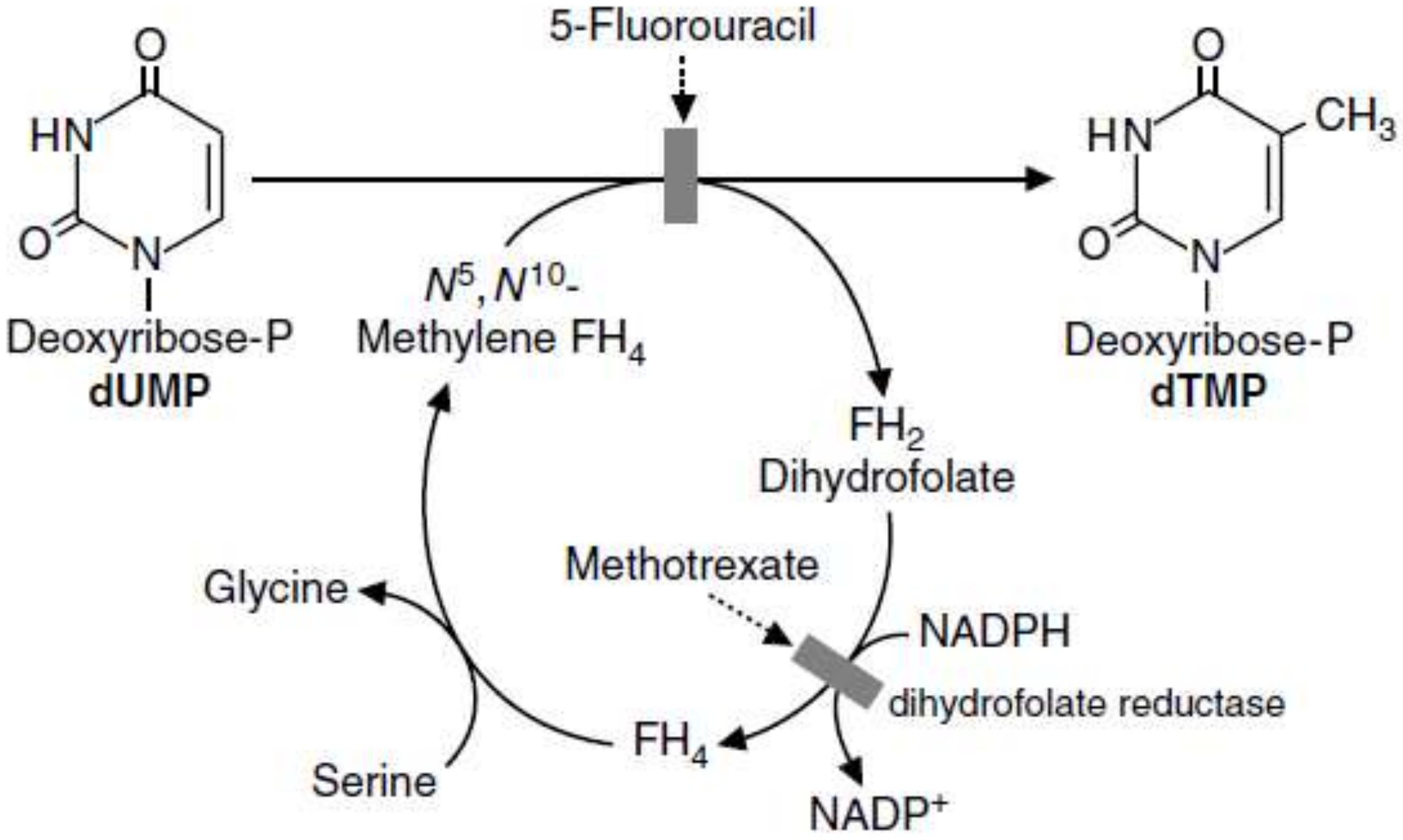
) to purine bases (adenine and guanine) to produce carbons C2 and C8 of the **purine ring.**

Therefore, FH4 is required for cell division thus compounds that inhibit formation of tetrahydrofolates will block purine synthesis and thus have been used in cancer chemotherapy.

3. Transfer a one-carbon group to the amino acid **glycine** to form **serine.**

Synthesis of dTMP from dUMP

- Transfer of a one-carbon unit from N5, N10 methhylene FH4 to dUMP to form dTMP.
- FH4 is oxidized to FH2 in this reaction.
- FH2 is reduced to FH4 by dihydrofolate reductase and FH4 is converted to N5, N10 methylene FH4 using serine as a carbon
- 5-fluorouracil (5-FU) and methotrexate are chemotherapy medication used to treat cancer.



Folate deficiency

Causes of folate deficiency, include:

1. Inadequate folate in dietary intake.

2. Folate is absorbed in the jejunum thus some diseases to small intestine can inhibit folate absorption resulting in a deficiency.

3. Some drugs can inhibit folate absorption or conversation to its active form

4. Congenital deficiencies of enzymes required in folate metabolism

5. Vitamin B-12 deficiency: vitamin B12 is required by methionine synthase for methyl group removal from N5-methyl FH4. Thus, if vitamin B12 is deficient N5-methyl FH4 will accumulate. Eventually most folate forms in the body will become "trapped" in the N5-methyl form. A functional folate deficiency results because the carbons cannot be removed from the folate.

6. Alcoholism is a significant cause of folate deficiency.

7. Pregnancy can also result in folate deficiency.

Complications of folate-deficiency

Untreated folate deficiency can lead to:

1. Megaloblastic anemia (also known as macrocytic anemia) characterized by reduction in the number of mature healthy red blood cells as well as the presence of unusually large, abnormal and poorly developed erythrocytes (megaloblasts). This condition is due to impaired DNA synthesis, which inhibits nuclear division.

2. Neural tube defect: (neural tube forms the early brain and spine) which is caused by folate-deficiency during pregnancy.

3. Cognitive impairment (a person has trouble remembering, learning new things), dementia, depression

Vitamin B12 (Cobalamin)

- Vitamin B12 is produced by bacteria, it cannot be synthesized by plants or animals.
- The major source of vitamin B12 is dietary meat, liver, eggs, dairy products, fish, poultry, and seafood.
- The animals that serve as the source of these foods obtain B12 mainly from the bacteria in their food supply.
- Because vitamin B12 contains the mineral cobalt it is called <u>cobalamins</u>

Vitamin B12 structure

1. Corrin ring: is made up from four pyrrole rings which is similar to the porphyrin ring found in heme.

2. Cobalt: is held in the center of the corrin ring by six coordination bonds (covalent bond) they are:

A. Four bonds with the nitrogen of corrin ring.

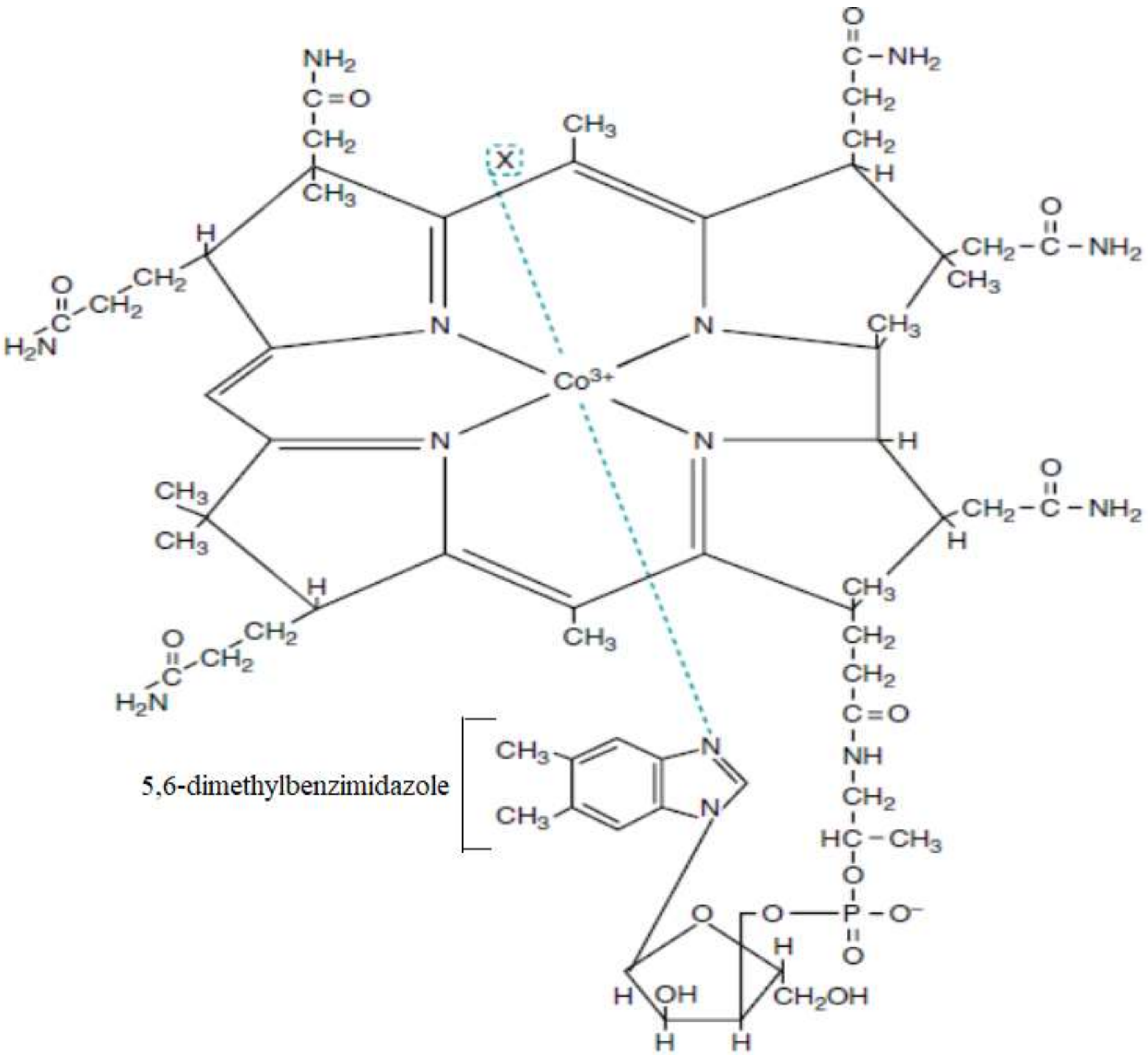
B. A bond with the nitrogen of 5,6-dimethylbenzimidazole

C. A bond with the **X which could be:**

- 5-deoxyadenosine in **5**-deoxyadenosylcobalamin
- CH3 in methylcobalamin;
- OH in hydroxycobalamin
- CN in cyanocobalamin

Methylcobalamin and 5-deoxyadenosylcobalamin are the metabolically active forms of vitamin B12.

B12 structure



Absorption of Vitamin B12

The ingested B12 can exist in two forms, free or bound to dietary proteins:

A. **Free B12** binds directly to transcobalamin I (also known as R-binder and haptocorrins), which are secreted by salivary glands and the gastric mucosal cells within the stomach and will remain in the bound form with an R-binder until it reaches the duodenum in the small intestine

B. **B12 bound to protein** must be released from the proteins by the action of digestive proteases both in the stomach and small intestine. Once the B12 is released from its bound protein, it will bind to the transcobalamin I. **Then:**

1. In the small intestine, the pancreatic proteases digest the R-binder.

2. The released B12 then binds to intrinsic factor which is a glycoprotein secreted by the parietal cells of the stomach.

3. The intrinsic factor–B12 complex bind to receptors on the ileum, which allow absorption of B12.

4. The absorbed vitamin B12 then binds to transcobalamin II where the liver takes up approximately 50% of the vitamin B12, and the remainder is transported to other tissues.

The amount of the vitamin stored in the liver is large enough that 3 to 6 years pass before symptoms of a dietary deficiency occur.

Reactions stimulated by Vitamin B12 in human body

Vitamin B12 is involved in two reactions in the body:

1. Methylation of homocysteine to methionine: this is important for DNA synthesis, myelin synthesis, neurotransmitters & brain metabolism and growth.

Homocysteine is an amino acid. Vitamins B12, B6 and folate break down homocysteine to create other chemicals your body needs. High homocysteine levels may mean you have a vitamin deficiency. Without treatment, elevated homocysteine increases your risks for dementia, heart disease and stroke.

2. Conversion of L-methylmalonyl CoA to succinyl CoA.

This biochemical reaction is important for the production of energy from fats and proteins.

This reaction is catalyzed by the enzyme methylmalonyl-CoA mutase (mitochondrial enzyme) which is a vitamin B_{12}-dependent enzyme.

Causes of v**itamin B12 Deficiency**

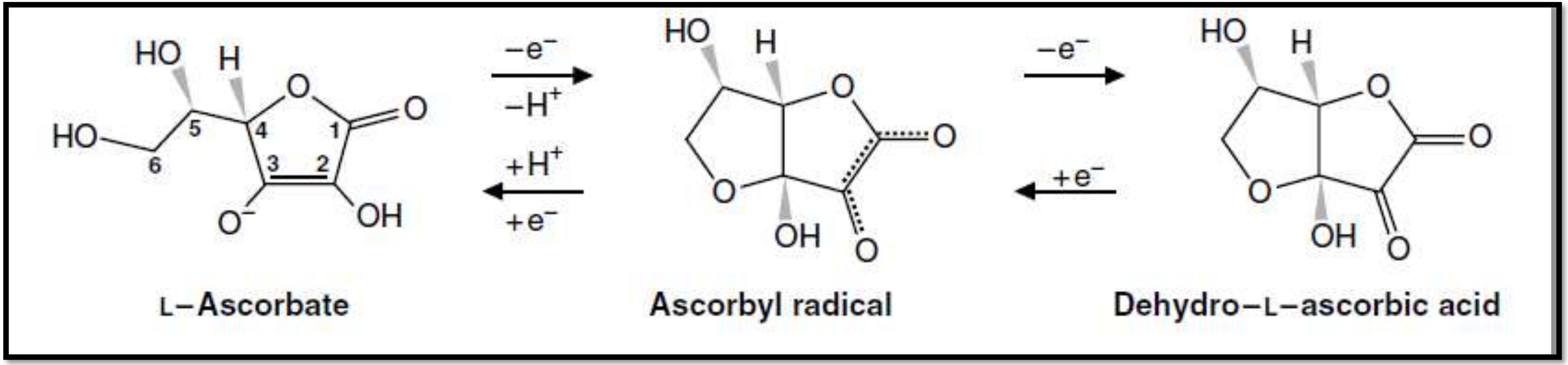
1. Pernicious anemia: is an autoimmune disease that cause the destruction of the gastric parietal cells that are responsible for the synthesis of intrinsic factor thus the body can’t absorb vitamin B12 correctly due to lack of intrinsic factor which leads to anemia and other problems.
2. Surgery in the gastrointestinal tract
3. Prolonged use of certain medications
4. Dietary deficiency

Symptoms of vitamin B12 deficiency include tingling and numbness in the extremities, nerve damage, and memory loss.

Vitamin C (L-ascorbic acid)

- The active form of vitamin C ($C_6H_8O_6$) is ascorbate.
- Humans are unable to synthesize vitamin C and can’t store it well so it is an essential dietary component
- Found in citrus fruits, berries, potatoes, tomatoes, peppers and others
- **The main function of ascorbate is**

1. A reducing agent (donating electrons) in many different reactions.
2. Biosynthesis of collagen.
3. Absorption of dietary iron from the intestine
4. Regenerate the reduced form of vitamin E through donating electrons



- L-Ascorbate (the reduced form) donates single electrons to free radicals in two steps as it is oxidized to dehydro-L-ascorbic acid.
- Its principle role in free radical defense is probably regeneration of vitamin E. However, it also may react with radicals.
- Vitamin C deficiency is associated with defective connective tissue, particularly in wound healing.
- A deficiency of ascorbic acid results in scurvy, a disease characterized by sore, spongy gums, loose teeth, fragile blood vessels, swollen joints, and anemia. Many of the deficiency symptoms can be explained by a deficiency in the hydroxylation of collagen (hydroxylation of proline residues), resulting in defective connective tissue